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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/935,124	08/21/2001	James B. Lorens	021044-000210US	8377

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EXAMINER	
HADDAD, MAHER M	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 01/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/935,124	LORENS ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,14-16,19 and 28-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *31* is/are allowed.

6)☒ Claim(s) *1,6,14-15,19 and 28-30* is/are rejected.

7)☐ Claim(s) *16* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/05 has been entered.

2. Claims 1, 6, 14-16, 19 and 28-31 are pending.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 6, 14-15, 19 and 28-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying a compound that modulates angiogenesis comprising contacting the compound with a cell expressing the ILKAP polypeptide of SEQ ID NO: 2 and determining the angiogenic or loss of angiogenesis phenotypic effect of the compound upon the cell expressing the ILKAP polypeptide, whereby the difference in the angiogenic or loss of angiogenesis effect as compared to the angiogenic or loss of angiogenesis effect in the absence of the compound indicates that the compound modulates angiogenesis. does not reasonably provide **enablement** for a method for identifying a compound that modulates angiogenesis comprising contacting the compound with a cell expressing an ILKAP polypeptide , wherein the ILKAP polypeptide "has at least 90% identity to an amino acid sequence of SEQ ID NO:2", and wherein the ILKAP polypeptide has an anti-angiogenic phenotype in claim 1, wherein the ILDAMP polypeptide "has at least 95% identity to an amino acid sequence of SEQ ID NO: 2" in claim 28, wherein the ILKAP polypeptide has at least 90% identity to the amino acid sequence of SEQ ID NO:2 over the entire length in claim 30. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons set forth in the previous Office Actions mailed 6/03/04 and 1/24/05.

At issue is the ILKAP polypeptide that "has at least 90/95% identity to an amino acid sequence of SEQ ID NO: 2" in claims 1, 28 and 30.

Applicant's arguments, filed 1/31/05, have been fully considered, but have not been found convincing.

Applicant draws the Examiner's attention to the *Ex parte Sun*, Appeal No. 2003-1993. Applicant contends that In *Sun,* the board found that claims directed to sequences with 80% identity to a reference sequence were enabled because the supporting specification provided a single reference sequence and an assay for activity of the encoded protein.

Applicant appears to mischaracterize the Board of Patent Appeals and Interference conclusion. In *Sun*, the claims are directed to a nucleic acid sequence encoding a novel maize homology of WEE1, a protein known in the art to be involved in cell cycle regulation and to nucleotide sequences having at least 80% identity with the coding sequence of the novel WEE1 protein. The Examiner in *Sun*, rejected the claims on the ground that they failed to satisfy the enablement and written description requirements of 112(1) paragraph. To support the rejections, the Examiner cited a prior-art reference that taught that a particular region of the WEE1 protein was critical for function. Based on this art, the Examiner concluded that alteration to this critical region could affect the function of the protein, and that one of skill in the art would not be able to predict the structure and function of sequence variations of the novel protein. However, the instant case, (1) the claims are directed to the use of a ILKAP polypeptide that has at least 90% identity to an amino acid sequence of SEQ ID NO: 2. (2) Neither the art nor the specification teaches a particular region of the ILKAP is critical for modulating angiogenesis function that one skilled in the art would avoid the said critical region. (3) The specification fails to disclose that the conserved serine/threonine phosphatase catalytic region of ILKAP is critical to the angiogenesis of activity of the SEQ ID NO:2 so that the skilled artisan would recognize that modification of the conserved serine/threonine phosphatase catalytic region would be most likely to have a detrimental effect on the ILKAP activity, hence avoid such modification in said region. Therefore *In Ex Parte Sun* dose not address the issue at hands and considered irrelevant to the claimed invention.

Applicant refers to the Declaration of Dr. Sacha Holland asserts that the specification and the knowledge of those of skill at the art at the time of filing, identification of functional ILKAP polypeptides with 90% identity to SEQ ID NO:2 was routine at the time of filing and that undue experimentation is not required by those skill to practice the claimed invention. Applicant's arguments the Declaration of Dr. Sacha Holland have been fully considered but not deemed persuasive and nor is the declaration sufficient to overcome the rejection when weighed within the whole body of evidence on this issue. First, it should be noted that Dr. Holland is an associate director for the Angiogenesis program at Rigel Pharmaceuticals, Inc., the real party in interest in this application, and thus is a concerned party. Such ex parte affidavit must be closely scrutinized and weighed with care, it being kept in mind that they may unconsciously and unintentionally be colored as a result of enthusiasm for the subject matter of the application. However, it is not to be disregarded for that reason alone and may be relied on when sufficiently convincing, see *Ex parte Coleman*, 29 USPQ 378,. *In re Mckenna et al.*, 97USPQ, *Bullard&Co.* V. Coe, 64, USPQ 359. Second, it is difficult to determine whether or not Dr. Holland's statements, referred to in Applicant's response, should be viewed as statements of fact, or of opinion, or of mere allegation. Affidavits or Declaration are provided as evidence and must set forth facts, not merely conclusion, *In re Pike et al.,* 84 USPQ235. Although in some cases it is appropriate to provide the reasoned opinion of an expert. In the instant case, Dr. Holland is unquestionably an expert, but absent evidence to the contrary, his statements must be considered, as most, to be his opinions because there does not appear to be any evidence of the use, as claimed, of the polypeptides that have at least 90% identity to an amino acid sequence of SEQ ID

NO:2. Further, these opinions appear to be totally unsupported and uncorroborated, thus they cannot be considered reasoned opinions and are therefore simply allegations. The weight given to an affidavit or declaration depends on whether it presents allegations, opinions or facts. Generally facts are the most probative, opinions are less probative and mere allegations are not probative, see *In re Knowtton*, 183 USPQ 33, 37; *In re Brandstadter*, 179 USPQ 286. The statements, referred to by Applicant, in the declaration appear to occupy some sort of middle ground between opinion and allegation and cannot be given much weight. The Declaration under paragraph 6, states that Leug-Hagesteijn et al (2001) references disclosing that the ILKAP protein is a serin/threonine phosphatase. Further, said declaration states that the reference discloses sequence analysis and alignments between the ILKAP protein and previously indentified members of the protein phosphatase 2C (PP2C) family. The declaration asserts that the reference provides experimental evidence of the function of the ILKAP protein by phosphatase assays. Also, the declaration states that the reference also confirms the sequence-based prediction of structure by demonstrating that mutation of a conserved active site, DGH, identified through the sequence alignments, abolished the phosphatase activity of the ILKAP protein. The Declaration on page 3, under paragraph 6, state that PP2C family of protein is well conserved and well understood. The Declaration points to the catalytic domain of SEQ ID NO:2 is 99.6% aligned with the catalytic domain of CD00143. The declaration indicates that the alignment identifies amino acid residues that are conserved between the ILKAP protein and cd00143.

However, neither Leug-Hagesteijn et al nor Applicant's specification establishes that the angiogenesis activity is mediated by modulation of ILK-mediated GSK3β signaling pathway (glycogen synthase kinase 3 β) that one skilled in the art would avoid the phosphatase activity of the ILKAP protein region in screening for the at least 90% identity sequences. The declaration is silent about the relationship between αvβ3 integrin surface expression and such phosphatase activity of the ILKAP protein in angiogenesis. The conserved catalytic domain of cd001434, has not been shown to have an angiogenic activity, even though it has 99.6% alignment with the catalytic domain of SEQ ID NO: 2, i.e., the catalytic domain of SEQ ID NO: 2 is not critical for its angiogenic activity. Therefore, there is no structure and function correlation between the catalytic domain and the angiogenic activity of the ILKAP protein.

Under paragraph 7 of the declaration, Dr. Holland states that based on the experimental results and alignments of ILKAP disclosed in Leung-Hagesteijn et al and the alignments of the ILKAP amino acid sequence wit PP2C conserved database domains, those of skill would be able to determine which ILKAP amino acids are most likely to require conservation to preserve function of the protein. However, there is tremendous variability in the importance of individual amino acids in protein sequences. Since the catalytic domain has not been shown to be a key determinants of activity of ILKAP in angiogenesis, residue substitutions that are conservative (e.g., Glu in equilibrium Asp, Asn in equilibrium Asp, Ile in equilibrium Leu, Lys in equilibrium Arg and Ala in equilibrium Gly) can have severe phenotypic effects. There is no simple way to infer the likely effect of an amino acid substitution on the basis of sequence information alone. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex.

While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al 1990, Science 247:1306-1310, especially p. 1306, col., 2, paragraph 2, of record). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g., such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in theses positions.

Although the declaration provides the suggestion that such variants can be obtained, this is not adequate guidance as the nature of active variants that may be constructed, but is merely an invitation to the artisan to sue the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues, therefore substitution of non-essential residues can often destroy activity.

In the Declaration under paragraphs 9-11, Dr. Holland disagrees with the analysis of the Office Action with respect to the teachings of Atwood, Skolnick et al and Metzler et al. The declaration states that both Atwood and Skolnick attempt to demonstrate the methods to identify a protein function base solely on comparison of an unknown amino acid sequence to known amino acid sequences with known functions are "unreliable" (Atwood), or inadequate" (Skolnick). The Declaration states that said references discuss only the problems of assigning function to a previously unknown protein based solely on sequence comparisons and lacking experimental evidence of function. The Dr. Holland contends that this type of analysis is not relevant to the claimed invention which recites use of ILKAP polypeptides. The specification and the information available at the time of filing provide experimental evidence of the function for the recited ILKAP proteins. The ILKAP protein has serine/threonine phosphatase activity, as disclosed in Leung-Hagesteijn et al. Example 1 of the specification provides experimental evidence of the angiogenic activity of the ILKAP protein. As the function of the ILKAP protein has been experimentally determined and assays to measure those function are known and routine, those of skill are able to identify functional variants of the ILKAP protein of SEQ ID NO: 2. Dr. Holland concluded that neither Atwood nor Skolnick teachings apply to the claimed invention.

The art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases and recognized that it was unpredictable if any functional activity will be shared by two polypeptides having less than 100% identity over the full length of their sequences. While the ILKAP protein has a partial PP2C-like phosphatase

domain, there is no described or art-recognized correlation or relationship between the structure of the invention, the PP2C-like phosphatase domain and it's anti-angiogenic function, the feature deemed essential to the instant invention. Further, the specification on page 44, under example 1 discloses that this clone, designated C1, encoded a partial PP2C-like phosphatase domain. BLAST analysis revealed a single Genbank entry without correlated function. The specification establishes that structural similarity among PP2C phosphatase is not predictive of functional similarity. Knowing this, the skilled artisan would have reason to believe that the claimed use of polypeptides that are among the 30-50% of polypeptides described by Atwood and Skolnick et al. as those whose functions cannot be predicted and must be determined empirically.

Regarding Metzler et al., Dr. Holland points that all of the mutations were made in residues that were highly conserved in CTLA4 family polypeptides and would therefore be expected. Dr. Holland concludes that Metzler et al demonstrates that modification of proteins, including the ILFKAP protein, can be done by those of skill with only routine experimentation.

However, the claims in the instant case are to a genus not to a single variant, such a genus not being supported by the specification. A polypeptide 90% identical to SEQ ID NO:2 would have as many as 39 amino acids substitutions relative to SEQ ID NO:2. Thus the expectation that any given artificially synthesized polypeptide that is 90% identical to SEQ ID NO:2 would be functional is astronomically low. No evidence has been put forth to support Dr. Holland's conclusion referred to above and the analysis made in rejection. The specification which has failed to disclose even a single modification, has failed to provide an enabling disclosure for the claimed genus.

5. Claims 1, 6, 14-15, 19 and 28-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a method for identifying a compound that modulates angiogenesis comprising contacting the compound with a cell expressing the ILKAP polypeptide of SEQ ID NO: 2 and determining the angiogenic or loss of angiogenesis phenotypic effect of the compound upon the cell expressing the ILKAP polypeptide, whereby the difference in the angiogenic or loss of angiogenesis effect as compared to the angiogenic or loss of angiogenesis effect in the absence of the compound indicates that the compound modulates angiogenesis.

Applicant is not in possession of a method for identifying a compound that modulates angiogenesis comprising contacting the compound with a cell expressing an ILKAP polypeptide , wherein the ILKAP polypeptide "has at least 90% identity to an amino acid sequence of SEQ ID NO:2", and wherein the ILKAP polypeptide has an anti-angiogenic phenotype in claim 1, wherein the ILDAMP polypeptide "has at least 95% identity to an amino acid sequence of SEQ ID NO: 2" in claim 28, wherein the ILKAP polypeptide has at least 90% identity to the amino acid sequence of SEQ ID NO:2 over the entire length in claim 30.

Neither the exemplary embodiments nor the specification's general method appears to describe structural features, in structural terms, that are common to the genus. That is, the specification provides neither a representative number of species (ILKAP polypeptides) to describe the claimed genus, nor does it provide a description of structural features that are common to species (ILKAP polypeptides). As discussed above, the specification provides no structural description of ILKAP polypeptides that have at least 90% identity to an amino acid sequence of SEQ ID NO: 2 other than ones specifically exemplified; in essence, the specification simply directs those skilled in the art to go figure out for themselves what the claimed ILKAP polypeptides that have at least 90% identity to an amino acid sequence of SEQ ID NO: 2 looks like. The specification's disclosure is inadequate to describe the claimed genus of ILKAP polypeptides that have at least 90% identity to an amino acid sequence of SEQ ID NO: 2.

Applicant has disclosed only amino acid of SEQ ID NO: 2; therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

6. Claim 16 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

7. Claim 31 is allowable.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

December 30, 2005

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